Immunotherapy and Cancer

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Disclosures

• No financial relationship with any drug company
• Own stock in a variety of biotech companies
What Happened To The Swim Lanes??

Agenda

- History of Cancer and Cancer Therapy
- Immune System’s Role in Cancer
- Immunotherapy in Cancer Treatment
- Examples of Existing Drugs
- New and Emerging Classes
- Some Individual Drugs
- Questions
The Changing World of Oncology

- Surgery
- Radiation
- Chemotherapy
- Targeted Therapy
- Immuno-Oncology or I-O

Cancer

- Second Leading Cause of Death in US
- Egyptian mummies
- Ancient manuscripts: 1600 B.C.
- Hippocrates (460-370 B.C.): Karkinos
- 1900’s Oncogenes and tumor suppressor genes were discovered
History of Cancer Therapy

1500 B.C.: Surgery
1896: Wilhelm Conrad Roentgen: Radiation

1940’s Sailors exposed to Mustard Gas… Leukemia

1950-1980’s Chemotherapies and combos:
Methotrexate,
Alkaloids (vinblastine, vincristine)
Purine analogues (6-mercaptopurine)
Taxanes (Pacific Yew tree)
Camptothecins inhibits topoisomerase (DNA unwinding)
Platinum compounds (serendipity)
Anthracyclines, epidophyllotoxins
Anti-hormonal therapies

1990-2000’s Targeted Therapies

Tyrosine Kinase Inhibitors:
Gleevec, imatinib
Iressa, gefitinib
Tarceva, erlotinib
Nexavar, sorafenib
Sutent, sunitinib
Sprycel, dasatinib
Tykerb, lapatinib
Tasigna, nilotinib
History of Cancer Therapy

1990-2000’s Targeted Therapies:

Serine/threonine kinase inhibitors
- Afinitor, everolimus
- Zelboraf, vemurafenib
- Mekinist, trametinib

Monoclonal Antibodies
- Rituxan, rituximab
- Herceptin, trastuzumab
- Campath, alemtuzumab
- Erbitux, cetuximab
- Vectibix, pantimumab
- Avastin, bevacizumab
- Yervoy, ipilimumab

Now: Immuno-Oncology
History of Immuno-oncology

- Late 19th century

- William B. Coley demonstrated the importance of activating the immune system in a cancer patient by injecting a live culture of bacteria into the tumor

Immune System in Oncology

- The entire immune system participates to help defend the body from the tumor;
- Innate immunity: natural killer cells or NK cells,
  - macrophages
  - dendritic cells
  - T- and B cells
  - cytokines
- Adaptive immune system
  - CD4+ helper T cells,
  - CD8+ cytotoxic T cells,
  - antibodies.
Basic Immunology

The innate response is the rapid recognition and eradication of invading pathogens (macrophages, monocytes, eosinophils, NK cells) and soluble mediators (activation of the complement cascade and acute phase reactants).

Activation of the innate response triggers the expression of costimulatory molecules and cytokines that allows for the specific adaptive response by cellular (T and B cells) and humoral elements.

Activation requires antigenic fragments be presented by MHC to antigen specific receptors on cytotoxic (CD8) T cells.

I-O

• Is the most disruptive approach to oncology in the past several decades
Some Basics

• The immune system is a series of checks and balances
  – Surveillance versus Permissive
• Programmed Cell Death-1 (PD-1)
• Programmed Cell Death Ligand-1 (PD-L1)
• T-lymphocyte-associated antigen-4 (CTLA-4)

Cancer: A Genetic Disease

• The result of multiple acquired genetic mutations to a series of normal cellular functions that occur inappropriately
• Tumor cells have accumulated enough mutations to overcome the natural ability of the body to prevent the growth of “non-self”

Foundation of Personalized Medicine
Limitation: Rapid Resistance
Cancer: An Immune Disorder

• Immunotherapy is a common denominator that can activate the immune system against a variety of proteins
• The adaptive immune system can keep pace with the tumor as it changes over time
• T cells $10^{18}$
• Antibodies $10^{22}$
• Can distinguish change over time
• Memory

Immunotherapy

• Therapies that activate the immune system to target tumors are a theoretically attractive approach for cancer management
• Developmental hurdles
  – lack of reliable biomarker
  – antigenic similarity of tumor cells and normal cells
  – the immunosuppressive nature of the tumor environment
Mutational Burden a Factor?

- Prevalence of somatic mutations higher in some cancers: melanoma and Lung\(^1\)
- In both, response to I-O best in patients with high mutational load \(^2,3\)
- Fewer immunogenic mutations expected in non-smokers and ALK/EGFR driven tumors \(^2\)

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1 Alexandrov LB et.al. Nature 2013;500:415-421
2 Rizvi NA, et.al. Science 2015;348:124-128
BUT…

• Hodgkin lymphoma has an 80% response rate with nivolumab yet mutational burden is not very high.

• So: Area Needs Study

Measuring Efficacy in Cancer
RECIST

- Response Evaluation Criteria in Solid Tumors
- Tumor-centric, not patient-centric
- Primary Measurements: CT and MRI
- Response Criteria
  - Complete Response: disappearance of all target lesions
  - Partial Response: $\geq 30\%$ decrease in sum of longest diameter (LD)
  - Stable Disease: neither larger or smaller
  - Progressive Disease: $\geq 20\%$ increase in sum of LD

Cancer Progression

- If a tumor increases in number or size, it is deemed to have progressed
- Traditional chemotherapy follows a “front-load” response…
  - (or at least typically)
- Once a tumor progresses, continuing current therapy is questioned
- But, what about when a checkpoint inhibitor is used?
Don’t Let Facts Get In The Way Of Clinical Judgment!

Pseudo-Progression

• Lymphocytes infiltrate a tumor
• Radiologic image enlarges
• Appears to be progression

• Occasionally, new nodules appear
  – Were undetectable prior to checkpoint inhibitor
Pseudo-Progression

- Originally described in the setting of GBM
- Now routinely observed in melanoma and lung cancer
- YouTube: >150 different videos

Pseudo-Progression

- Challenges traditional RECIST criteria
- Destroys typical managed care processes
- Pits Hope against Facts

Don’t Let Facts Get in the Way of Clinical Judgment!
Size Versus Other Clinical Attributes

Bi-dimensional Radiological Response Versus Rapidity and Durability

Demonstrates the Argument of: Facts versus Clinical Judgment

Immune Related (ir) Criteria

• irComplete Response
  – complete disappearance of all lesions measured or unmeasured
• irPartial Response
  – 50% drop in tumor burden
• irProgressive Disease
  – 25% increase in tumor burden from lowest level recorded
• irStable: all else
Comparison: RECIST-irRC Criteria*

<table>
<thead>
<tr>
<th>RECIST</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, measurable lesions (i.e. ≥5 x 5 mm)</td>
<td>Always represent PD</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (i.e. &lt;5 x 5 mm)</td>
<td>Always represent PD</td>
</tr>
<tr>
<td>Non-index lesions</td>
<td>Changes contribute to defining BOR of CR, PR, SD, and PD</td>
</tr>
</tbody>
</table>

**Complete Response (CR)**
- Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.
- Disappearance of all lesions in two consecutive observations not less than 4 weeks apart.

**Partial Response (PR)**
- At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters.
- ≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart.

**Stable Disease (SD)**
- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- 50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir.

**Progressive Disease (PD)**
- Sum of longest diameter (SLD) increased by at least 20% from the smallest value on study (including baseline, if that is the smallest).
- The SLD must also demonstrate an absolute increase of at least 5 mm (two lesions increasing from 2 mm to 3 mm, for example, does not qualify).
- At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart.

*Total Burden=SPD<sub>index lesions</sub> + SPD<sub>new, measurable lesions</sub>

Here in lies the rub

- From a given tumor burden, a shrinkage of 49% or an increase of 24% are considered irStable.
- Are you measuring swelling… or real tumor.
- Confounding issue to say the least.
Pseudo-Progression versus Progression

• May lead to the continuation an ineffective therapy
• May lead to the discontinuation of an effective therapy
• May delay palliative care

Potential Targets
T Cell Targets For Immunoregulatory Antibody Therapy

Normal Immune Function

- Relies on the PD system and CTLA mechanisms (in part) to kill tumor cells as they develop
- If a tumor cell develops a PD or CTLA pathway, it can evade detection and avoid destruction
Desirable Immune Function

Chemo/Radiation leads to cell death which releases antigens...

PD-1 and PD-L1 = Cloaking

- PD-1 is a receptor on a T cell
- PD-L1 is a ligand (or connector) for PD-1 on cells; **cancer and non-cancer**
- If a cell does not have PD-L1, the T cell can kill it
- If a cell has PD-L1, it will tell the T cell to ignore it…It turns off the T cell

- Tumors that possess the genetic makeup to manipulate the PD system can effectively evade the immune system
Theory

- If we could somehow block the PD-1 or the PD-L1, we could get the T cell to kill the tumor cell
- Hence the strategy to develop antibodies against these two molecules
- Goal: Disable the inhibition
PD-L1 Biomarkers

• A Way to Quantify the PD-L1 receptor

• “For each the known biomarker assays in development, there is a different monoclonal IHC antibody clone”
• “Each test requires proprietary staining platforms and uses different definitions of a “positive” test for PD-L1 expression”
• “There are still considerable gaps in our knowledge of the technical aspects of these tests, and of the biological implications and associations of PD-L1 expression in NSCLC…”

Identifying Predictor(s) of Response

Responses are higher in PD-L1+ tumors but seen in PD-L1- tumors

Challenges

PD-L1 IHC Expression By Various Assays

<table>
<thead>
<tr>
<th>Tumor</th>
<th>GNE</th>
<th>DAKO 28-8</th>
<th>Merck CC23</th>
<th>5H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>40%</td>
<td>45%</td>
<td>71%</td>
<td>42%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>45-50%</td>
<td>49%</td>
<td>45%</td>
<td>25%</td>
</tr>
<tr>
<td>Renal</td>
<td>20%</td>
<td>49%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>21%</td>
<td>49%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Head And Neck</td>
<td>31%</td>
<td>49%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>25%</td>
<td>49%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

- No validated assay
- Variable cut off levels for positivity

Emerging data suggest that patients whose tumors overexpress PD-L1 by IHC have improved clinical outcomes with anti-PD-1–directed therapy, but the presence of robust responses in some patients with low levels of expression of these markers complicates the issue of PD-L1 as an exclusionary predictive biomarker.

Approved Immuno-Oncology Therapies

- **CTLA:**
  - ipilimumab: Yervoy (BMS)
- **PD-1**
  - pembrulizumab: Keytruda (Merck)
  - nivolumab: Opdivo, (BMS)
- **PDL-1**
  - atezolizumab: Tecentriq, (Genentech)
Approved Therapies

ipilimumab, Yervoy
- Cytotoxic t-lymphocytes (CTL’s) can recognize and destroy cancer cells
- Some cancers have an inhibitory mechanism that interrupts this destruction
- Ipilimumab targets the CTLA-4 protein receptor that down-regulates the CTL’s
- Approved for late-stage melanoma

pembrolizumab, Keytruda: PD-1
- Unresectable or metastatic melanoma
- Metastatic NSCLC
- Head and neck squamous cell carcinoma (HNSCC)
  - Q 3 weeks until progression or up to 24 months for NSCLC and HNSCC
nivolumab, Opdivo: PD-1

- **Melanoma**: BRAF V600 wild-type unresectable or metastatic melanoma.
- **in combination with ipilimumab for unresectable or NSCLC**: Metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Note: EGFR and ALK
- **Renal cell carcinoma (RCC)** who have received prior anti-angiogenic therapy.
- **Hodgkin lymphoma** (classical) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

Atezolizumab, Tecentriq: PD-L1

- Locally advanced or metastatic urothelial carcinoma
- Metastatic non-small cell lung cancer (NSCLC) who have progression during or following platinum-containing chemotherapy
Comparison of Therapeutic Antibodies Blocking PD-1/PDL-1 Interaction

IgG4 hinge mutant
- BMS Anti-PD-1
- Merck Anti-PD-1
- 40% reduced ADCC†
- Potential to deplete activated T cells and TILs and diminish activity
- Blocks PD-L1/PD-L2 interaction in lungs
- Potential for autoimmune pneumonitis

IgG1 Engineered
- Genentech Anti-PD-L1
- No ADCC†
- Decreased potential to deplete activated T cells and TILs
- Leaves PD-L1/PD-L2 interaction intact in lungs
- Decreased potential for autoimmune pneumonitis
- Blocks PD-L1/B7.1 interaction
- Potential for enhanced priming

Role of PD-1 in Suppressing Antitumor Immunity

- Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
- Binding to PD-L1 leaves PD-L1/PD-L2 interaction intact and may enhance efficacy and safety

Adapted from Spigel et al. Proc ASCO 2013;Abstract 8008.
Anti-PD-1 and Anti-PD-L1 mAbs block distinct interactions

**PD-1 Blockade of T CELL**

Blocks PD-L1 and PD-L2 binding to PD-1

PD-L1 can still engage B7-1

Anti-PD-1 and Anti-PD-L1 mAbs block distinct interactions

**PD-L1 Blockade of Tumor Cell**

Blocks PD-L1 binding to PD-1 and B7-1

PD-L2 can still engage PD-1
Adverse Events in Pivotal Trials

- **Nivolumab**: Pivotal phase 3 trial in advanced NSCLC
  - Most common: fatigue, pruritus, decreased appetite and asthenia
  - Also diarrhea, hypothyroidism, increased ALT and AST, pneumonitis (~3%)
- **Pembrolizumab**: Pivotal phase 3 trial in NSCLC
  - Most common: fatigue, pruritus, decreased appetite
  - Also, inflammatory or immune-mediated AEs, hypothyroidism, pneumonitis

For lung cancer, most bothersome AE:
  Pneumonitis ~4% of patients

Efficacy

• Tecentriq:
  • ORR for Urothelial Carcinoma
    – PD-L1 <5% = 9.5%
    – PD-L1 > 5% = 26.0%
  • NSCLC:
    • ORR: 15%
    • Overall Survival: 13.8 versus 9.6 Months (docetaxel)

Keytruda

• Melanoma (versus ipi)
  – ORR: 33% versus 12%

• NSCLC: (versus chemo)
  – Objective Response Rate: 45% versus 28%
  – PFS: 10.3 versus 6.0
**CheckMate 069: NIVO + IPI vs IPI in Untreated Advanced Melanoma (Phase 2)**

- 142 pts were randomized 2:1 to receive IPI with either NIVO or placebo every 3 weeks for 12 weeks, followed by NIVO or placebo every 2 weeks until progression or unacceptable toxicity
- Primary end point was ORR in pts with BRAF wild-type (n = 109)

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI + NIVO (n = 72)</td>
<td>60</td>
<td>17</td>
<td>8.9</td>
</tr>
<tr>
<td>IPI alone (n = 37)</td>
<td>11</td>
<td>0</td>
<td>4.7</td>
</tr>
</tbody>
</table>

- Grade 3/4 drug-related AEs: 51% with NIVO + IPI, 20% with IPI


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**CheckMate 017: Results in Squamous NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>NIVO (n = 135) (range)</th>
<th>DOC (n = 137) (range)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo, 95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.2 (7.3–13.3)</td>
<td>6.0 (5.1–7.3)</td>
<td>0.59 (0.44–0.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em> &lt; .001</td>
</tr>
<tr>
<td>Median PFS (mo, 95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.5 (2.1–4.9)</td>
<td>2.8 (2.1–3.5)</td>
<td>0.62 (0.47–0.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em> &lt; .001</td>
</tr>
<tr>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20%</td>
<td>9%</td>
<td><em>P</em> = .008</td>
</tr>
</tbody>
</table>

**Nivolumab is now approved for the treatment of both squamous and nonsquamous metastatic NSCLC**

b. OPDIVO® PI 2015.
Important Questions about Immune Checkpoint Inhibitors

- Anti-PD1 or Anti-PDL1
- Ideal dosing schedule and duration of therapy
- PDL1 status: should it guide treatment?
- Optimal Combinations of I-O drugs?
- What are the Mechanisms of Resistance?
- Adaptive Trials with interim analysis to allow accelerated patient access

Future Development
T Cell Targets For Immunoregulatory Antibody Therapy


Combined Immunomodulation

My Humble Opinion

• No better time in oncology, or medicine in general, than today.
• Exciting times for those suffering from cancer.

Totally unaffordable trends in cost for oncology care.

“Value” is an issue.

let me explain…

Thank You!

There is no danger of developing eye strain from looking at the bright side of things

Unknown
• http://www.fightcancerwithimmunotherapy.com/portals/1/Images/02_IMTY/bdyTab3Chart-04.png

• http://www.medscape.org/viewarticle/830857
Mechanism of action

IMMUNOMODULATORS


- Website: [http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources](http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources)
Ipilimumab and Nivolumab
Mechanisms of Action

- PD-1 expression on TILs is associated with decreased cytokine production and effector function\textsuperscript{1}
- Nivolumab is a fully human IgG4 immune checkpoint inhibitor antibody
  - Binds PD-1 receptors on T cells
  - Disrupts PD-L1/PD-L2 signaling to restore antitumor immunity\textsuperscript{2,4}
- Nivolumab and the anti-CTLA-4 antibody ipilimumab, enhance T-cell antitumor activity through distinct but complementary mechanisms\textsuperscript{1-3.5}
- The combination of nivolumab and ipilimumab has demonstrated deep and durable responses in solid tumors\textsuperscript{6,7}

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APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T cell receptor

Presented by Michael Overman at 2016 ASCO Annual Meeting